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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/771,503	01/26/2001	Henry Yue	PC-0027 US	6227
27904	7590	03/10/2004	EXAMINER	
INCYTE CORPORATION 3160 PORTER DRIVE PALO ALTO, CA 94304			CANELLA, KAREN A	
			ART UNIT	PAPER NUMBER
			1642	

DATE MAILED: 03/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/771,503

Applicant(s)

YUE ET AL.

Examiner

Karen A Canella

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☒ This action is FINAL. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 1-21 is/are pending in the application.
- 4a) Of the above claim(s) 14-21 is/are withdrawn from consideration.
- 5) ☐ Claim(s) 1 and 3-7 is/are allowed.
- 6) ☐ Claim(s) 2, 8-13 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date ____.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: ____.

DETAILED ACTION

1. Claims 1-4 and 11 have been amended. Claims 14-21, drawn to non-elected inventions, remain withdrawn from consideration. Claims 1-13 are under consideration.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

3. The rejection of claims 11 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained for reasons of record.

Claim 11 is drawn to a method for using a cDNA to detect expression of a nucleic acid in a sample comprising hybridizing the composition of claim 4 to a nucleic acid sample under conditions to form at least one hybridization complex; and detecting hybridization complex formation, wherein complex formation indicates expression of the nucleic acid in the sample, wherein the cDNA is differentially expressed when compared with a standard and diagnostic of colon cancer or colon polyps. The method is vague and indefinite in that there is no definition or limitation for "a standard"; and there is no active method step linking the outcome of comparison with said standard to the diagnosis of colon cancer or colon polyps.

Applicant argues that the meaning of the term "standard" is defined by specific examples in the specification at page 35, example XI which describe the preparation of matched normal and cancerous colon or colon polyp tissue. this has been considered but not found persuasive. The example cited by applicant is a preferred embodiment and cannot be considered as a definition for the term "standard".

4. The rejection of claim 2, 8-10, 12 and 13 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained for reasons of record.

(A)As drawn to polynucleotides comprising EST sequences

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Claim 2 is drawn to an isolated DNA comprising SEQ ID NO:3-5 or the complement of SEQ ID NO:3-5. SEQ ID NO:3-5 are partial DNA sequences consisting of residues 1-276, 1-497 and 1-606 of SEQ ID NO:2. Claim 2 is drawn to a genus of nucleic acids in that it encompasses any nucleic acid sequence that minimal comprises SEQ ID NO:3- within it, including any full gene which contains the sequence, and any fusion constructs. The specification does not address whether the partial cDNA sequences cross exon/intron splice junctions which would exclude the possibility of the claims reading on a full length gene. Therefore when given the broadest reasonable interpretation the claim encompasses full length genes and cDNAs that are not fully described. It is noted that the description of a full length open reading frame is not a description of a gene as eukaryotic genes are expected to have introns and regulatory regions, such as promoters.

A description of a genus of nucleic acids may be achieved by means of recitation of representative number of cDNAs defined by nucleotide sequence falling within the scope of the genus which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Here the specification discloses only SEQ ID NO:3-5 as structural features shared by members of the claimed genus. Since the claimed genus encompasses genes yet to be discovered, and DNA construct that encode fusion proteins, the structural features of SEQ ID NO:3-5 do not constitute a substantial portion of the claimed genus. Therefore, the disclosure of SEQ ID NO:3-5 does not provide an adequate description of the claimed genus. Amendment of product claims drawn to SEQ ID NO:3-5 to nucleic acids consisting of, rather than comprising, would obviate this part of the rejection.

Applicant has attempted to overcome this rejection by amending claim 3 to read an isolated DNA consisting of a nucleic acid sequence rather than comprising. however, claims 2(b) is still drawn to an isolated cDNA comprising a fragment of SEQ ID NO:2 selected from the group consisting of SEQ ID NO:4 and 5 or the complements of SEQ ID NO:4 and 5 and thus reads on isolated cDNA which minimally comprising SEQ ID NO:4 or 5.

(B)As drawn to a method of using a cDNA to detect expression of a nucleic acid, wherein said cDNA is not the complementary sequence to SEQ ID NO:2.

Applicants arguments have overcome this section of the rejection

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(C)As drawn to a method of using a cDNA to screen a plurality of molecules which specifically bind the cDNA (peptides, transcription factors).

Claim 12 is drawn to a method for using a cDNA to screen a plurality of molecules or compounds the method comprising combining the cDNA of claim 1 with a plurality of molecules under conditions to allow for specific binding, detecting the specific binding, thereby identifying a molecule of compound which specifically binds to the cDNA. Claims 13 embodies the molecules or compounds of DNA, RNA, peptide nuclei acids, artificial chromosomes, peptides or transcription factors. The claims rely on a genus of molecules and compounds which specifically bind to the cDNA of claim 1. The specification describes a method of detecting colon cancer or colon polyps wherein hybridization of a nucleic acid probe which binds to SEQ ID NO:1 is indicative of colon cancer or colon polyps. The specification does not describe any other active methods steps in which detection of a nucleic acid probe to the complement of SEQ ID NO:2 is indicative of colon cancer or colon polyps, or any other disease. One of skill in the art would conclude that applicant has not provided a representative number of species which anticipate the claimed genus, wherein the species comprise a method step for the detection of the complement of SEQ ID NO:2, nor are there a representative number of species of method steps for the detection of disease or pathological conditions beyond those of colon cancer or colon polyps. The general knowledge and skill in the art does not supplement the omission in the disclosure because specific not general guidance is what is needed. In reference to claims 12 and 13, the specification has not described any method steps wherein specific peptides or transcription factors are identified by binding to SEQ ID NO:2 or the complement of SEQ ID NO:2. It is well known in the art that DNA sequences comprising the complementary base part of a given sequence will form a hybridization with a given sequence under appropriate physical conditions. However, in the case of generic proteins and generic transcription factors as recited in the method limitation of claim 13, the general knowledge and skill in the art do not supplement the omitted description because there is no nexus between protein sequences which bind to DNA and transcription factor and the primary DNA sequence given by the nucleic acids which encode SEQ ID NO:1. Further the art defines a transcription factor as any of the multiple ancillary DNA-binding proteins which interact with the cis-regulatory DNA sequences to control gene expression (Reiger, Glossary of Genetics and Cytogenetics, 1991, page 481).

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The specification fails to disclose the cis-regulatory region of SEQ ID NO:2, which is commonly located upstream in the promoter region of the gene. The specification does not reduce to practice claim 13 and no peptides or transcription factors have been disclosed which have been isolated by the claimed method. Thus the specification does not provide adequate written description for claim 13 because disclosure of hybridization to DNA sequences does not anticipate method steps involving DNA-peptide binding or DNA-transcription factor-binding. One of skill in the art would reasonably conclude that applicant did not disclose a representative number of species representative of the claimed method with regard to method steps involving transcription factors. Claim 13 also carries the limitation of selecting "peptides" to allow for specific binding to the DNA comprising the nucleic acids encoding SEQ ID NO:1 or the complement of SEQ ID NO:1. The specification has not described any method steps wherein specific peptides were screened for binding to the cDNA of claim 1. Further, the art recognizes that there is no reliable nexus between the binding of a protein to a DNA sequence and the primary nucleotide sequence as exists for polynucleotide-polynucleotide binding. For instance, Saenger (Principles of Nucleic Acid Structure, 1984, pages 385-431) teaches that protein-nucleotide interactions depend on two main characteristics, the overall topology of the two partners and the specific interactions between individual nucleotide and protein main chain or side-chain atoms (page 408, lines 1-4) and that a wide range of protein-nucleotide interactions does exist wherein the nucleic acid interacts with the protein by means of both the amino acid side chains and the peptide functional groups (page 418, lines 8-13). More recent publications corroborate the teachings of Saenger, such as taught by Wolfe et al (Structure, 2001, Vol. 9, pp. 717-723) who teach that the interaction between zinc finger proteins and DNA is complex and reveals differences between the interaction of individual nucleotides and amino acid side chains and that the zinc-finger-DNA interaction cannot be determined by a "meaningful recognition code" of the nucleic acid even for zinc finger proteins which are known to bind to DNA. One of skill in the art would readily conclude that the description of a method wherein the nucleic acid of claim 1 is hybridized to a polynucleotide which hybridizes to the nucleic acid of SEQ ID NO:2 does not adequately anticipate claims 12-13 as drawn to a method of screening for proteins and transcription factors which bind to either SEQ ID NO:2 or the complement of SEQ ID NO:2.

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Applicant summarizes the examiners rejection by accurately stating that the "examiner appears to require that the method of claims 12 and 13 for identifying molecules or compounds that bind to either the cDNA encoding SEQ ID NO:1 or the its complement either be connected with colon cancer or colon polyps as described in claim 11. Applicants disagree with this interpretation stating that an adequate written description of a claimed method require a disclosure of the specific molecules or compounds and their specific mechanisms of interaction. this has been considered but not found persuasive. A method claim reliant upon the identity of a product cannot be adequately described if the product itself is not adequately described. applicant argues that ligands are further described in the specification at page 8, line 15-18 as any agent molecule or compound which will specifically bind to a polynucleotide or an epitope of a protein. applicant argues that the specification describes methods of screening for and purifying various molecules, compounds or ligand that bind a polynucleotide or protein at page 20, lines 12-31. this has been considered but not found persuasive. the findings in *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and *Enzo Biochem, Inc. V. Gen-Probe Inc.* are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Id.* At 1567, 43 USPQ2d at 1405. The court also stated that a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. *Id.* At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist,

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in the absence of knowledge as to what that material consists of, is not a description of that material." Id. In the instant case the "plurality of molecules" wherein said molecules are selected from the group consisting of DNA molecules, RNA molecules, peptide nucleic acids, artificial chromosome structure, peptides and transcription factors are not structurally described and the claim limitations rely only upon "naming a type of material generally known to exist".

5. The rejection of claims 8-11 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting colon cancer or colon polyps comprising the detection of SEQ ID NO:2, the complete complement of SEQ ID NO:2, the nucleic acids encoding SEQ ID NO:1, the complete complement of SEQ ID NO:1 in a sample of colon tissue, does not reasonably provide enablement for a method of detecting any other disease or condition comprising the detection of SEQ ID NO:2, the complement of SEQ ID NO:2, the nucleic acid sequences encoding SEQ ID NO:1, or the complete complement of SEQ ID NO:1 is maintained for reasons of record. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Claim 8 is drawn to a method for using a cDNA to detect expression of a nucleic acid in a sample comprising hybridizing the composition of claim 4 to nucleic acid in said sample. Thus, claim 8 is drawn in part to a method of using the nucleic acid encoding SEQ ID NO:1 for the detection of expression of nucleic acids within a sample. the specification has not provided guidance as to other diseases or conditions beyond those of colon cancer or colon polyps which would be indicative of the differential expression of the nucleic acids encoding SEQ ID NO:1 or the complement thereof. One of skill in the art would be subject to undue experimentation without reasonable expectation of success in order practice the broadly claimed methods.

Applicant disagree that the specification is not enabling for any use of the polynucleotide encoding SEQ ID NO:1. Applicant argues that the use of the claimed polynucleotides is not limited to the detection of colon cancer or polyps, and contends that either strand of the disclose polynucleotides is enabled for whatever reason the skilled artisan may choose. this has been considered but not found persuasive. In order for an invention to meet the requirement of 35 U.S.C. 112, first paragraph, the specification must divulge how to make and how to use the

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claimed invention. In the instant method claims, the specification has only enabled the scope of the claims for the detection of colon cancer or colon polyps. The examiner has removed rejections relating to the detection of only one strand of the polynucleotide with respect to the detection of colon cancer or colon polyps. However, when given the broadest reasonable interpretation the instant claims encompass the detection of a cDNA in any sample comprising hybridization with either strand of SEQ ID NO:1. The specification is only enabling for the diagnosis of colon cancer or colon polyps. No other specific, substantial and credible utility has been identified for the instant SEQ ID NO:2 or the polynucleotide encoding SEQ ID NO:1.

6. The rejection of claims 12 and 13 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of screening comprising the detection of DNA molecules, RNA molecules, peptide nucleic acids and artificial chromosome constructions which bind to the polynucleotides encoding SEQ ID NO:1 and the complete complement of SEQ ID NO:1 does not reasonably provide enablement for a method of screening for peptides or transcription factors which bind to the polynucleotides which encode SEQ ID NO:1 or the complete complement thereof, is maintained for reasons of record. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 12 is drawn to a method of using a cDNA to screen a plurality of molecules or compounds, the method comprising combining the cDNA of claim 1 with a plurality of molecules or compounds under conditions to allow for specific binding and detecting specific binding thereby identifying a molecule or compound which specifically binds to the cDNA. Claim 13 embodies the method of claim 12 wherein the molecules or compounds are selected from DNA molecules, RNA molecules, peptide nucleic acids, artificial chromosome constructions, peptides or transcription factors. The specification teaches only the binding of a nucleic acid sequence to the nucleic acids encoding SEQ ID NO:1 or SEQ ID NO:2, wherein detection of the hybridization complex is indicative of colon cancer or colon polyps. The species of DNA molecules, RNA molecules, peptide nucleic acids and artificial chromosome constructs are commensurate in scope with the teachings of the specification, with regard to the detection of the nucleic acids encoding SEQ ID NO:1 and colon cancer or colon polyps, however, the

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specification provides no teachings of how to use the broadly claimed molecules which bind to the complement of the nucleic acids which encode SEQ ID NO:1, nor how to use "peptides" and "transcription factors" which bind to a nucleic acid sequence comprising the polynucleotide of claim 1. As stated above, Reiger, (Glossary of Genetics and Cytogenetics, 1991, page 481). defines a transcription factor as any of the multiple ancillary DNA-binding proteins which interact with the cis-regulatory DNA sequences to control gene expression. The specification fails to disclose the cis-regulatory region of SEQ ID NO:2, which is commonly located upstream in the promoter region of the gene. The specification has failed to teach the sequence of a c-s-regulatory DNA sequence upstream of the protein coding sequence. With regard to "peptides" the specification has failed to identify a peptide binding sequence with the claimed DNA sequence and has not taught how to make or use peptides or transcription factors. Clearly, one of skill in the art would not know how to use the multitude of potential peptides that would bind to the claimed DNA, and the specification has failed to teach a single example of such. Further, the specification has failed to teach how to use a "transcription factor" isolated by the claimed method. It is noted in the art that although a limited number of transcription factors are correlated with cancerous cells, there is as of four years past the claimed priority date of the instant application no means of controlling specific transcription factor activity within the cells (abstract, Darnell, Nat Rev Cancer, 2002, Vol. 2, pp. 740-749). Further, section 2164.03 of the M.P.E.P. states

A single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements. In re Vickers, 141 F.2d 522, 526-27, 61 USPQ 122, 127 (CCPA 1944); In re Cook, 439 F.2d 730, 734, 169 USPQ 298, 301 (CCPA 1971). However, in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. In re Soll, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); In re Vaack, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work

Clearly, the disclosure that the hybridization complex between the nucleic acids which encode SEQ ID NO:1 and a labeled probe, wherein the level of hybridization complex is indicative of colon cancer or colon polyps is not commensurate in scope with the claimed method of using a cDNA for screening a plurality of molecules or compounds, wherein the only criteria of the assay is the detection of binding to either the nucleic acids which encode SEQ ID NO:1 or the complement thereof. As stated by the MPEP, the disclosure of a single species usually does not provide adequate basis to support generic claims. Claim 12 is generic because the only criteria of the assay is the binding to either the nucleic acids which encodes SEQ ID NO:1 or the complement thereof, without reference to colon cancer or colon polyps. Accordingly, there is no enablement for the broadly claimed method beyond the screening of molecules which hybridize to the nucleic acids which encode SEQ ID NO:1, wherein it is determined that the nucleic acids are indicative of colon cancer or colon polyps.

Applicant insists that the claimed methods is not limited in any way to a use in the detection and diagnosis of colon cancer or colon polyps, and that the identity of the molecules or compounds that specifically binds the claimed polynucleotides or their mechanisms of interaction need not be disclosed to sufficiently enable the practice of the claimed method. Applicant contends that the use of the molecules or compounds so identified is totally at the discretion of the skilled artisan. This has been considered but not found persuasive. The examiner again refers applicant to the statutory basis of 35 U.S.C. 112, first paragraph which states that the specification must teach how to make and how to use an invention. In the instant case, the specification does not teach how to use the peptides or transcription factors which would be isolated from the claimed screening methods. therefore, the specification is not enabling for how to use said method.

7. The rejection of claim 2(b) under 35 U.S.C. 102(b) as being anticipated by The New England Biolabs Catalog (1993-1994, page 91) is maintained for reasons of record. The New England Biolabs Catalog discloses random hexamers which will be complementary across their full length to the nucleic acids encoding SEQ ID NO:4 and 5. applicant argues that the random hexamers do not anticipate a polynucleotide completely complementary to the polynucleotide encoding SEQ ID NO:1, or to SEQ ID NO:2. this has been considered but not found persuasive,

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as claim 2(b) carries the limitation of complementary to SEQ ID NO:4 or 5 rather than completely complementary to SEQ ID NO:4 or 5.

8. All other rejections and objections as set forth in the previous Office action are withdrawn.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on (571)272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197-(toll-free).

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Karen A. Canella, Ph.D.

Primary EXaminer, Art Unit 1642

03/08/04

A handwritten signature in black ink, reading "Karen A. Canella". The signature is fluid and cursive, with the first name "Karen" and last name "Canella" clearly distinguishable.

KARENA. CANELLA PH.D
PRIMARY EXAMINER